REMARKS

Claims 1-28 and 34-43 are currently pending in the application. Claim 10 has been amended. Support for the amendment can be found on page 17, line 25 to page 18, line 10. Applicants respectfully assert that no new matter has been added and request reconsideration of the claims currently pending in the application.

Rejection under 35 U.S.C. § 103

On page 2 of the Office Action, claims 1-28 and 34-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ogle, et al.. (U.S. Patent No. 5,958,669) in view of Yang, et al.. (U.S. Patent No. 5,935,168). Applicants respectfully traverse the rejection.

Ogle et al. discloses a method and apparatus for crosslinking a tissue using a semi-permeable membrane for screening out crosslinking compounds or oligomers not having the desired molecular weight or size. See col. 1 line 47 to col. 2 line 57. As noted by the Examiner, the tissue can be fixed by crosslinking with crosslinking agents like glutaraldehyde. The crosslinking compounds, such as dialdehydes, can polymerize spontaneously in solution, generating oligomers of varying sizes or molecular weights. See col. 4, lines 1-9. By the screening method described, the oligomers having the correct molecular weight can pass through the screen to crosslink the tissue. See col. 5, lines 22-36.

Yang et al. discloses a tissue already crosslinked with glutaraldehyde to form a fixed tissue, the same as the crosslinked tissue discussed in Ogle et al.. See col. 3, lines 2-5. This crosslinked tissue is then reacted with a diamine to replace at least some of the carboxyl groups present on the collagen and/or elastin molecules with non-carboxyl side

groups. This replacement of the carboxyl groups does not affect the glutaraldehyde crosslinked portion. See col. 3, lines 2-17, and Figure 2. This is done because glutaraldehyde fixed tissue which contains collagen and/or elastin is prone to calcification. See col. 3, lines 2-11, and 44-64. Applicants respectfully submit that there is no bonding of the crosslinkers, such as glutaraldehyde, to bridge molecules, as the glutaraldehyde crosslinkers are already crosslinked to the tissue via the aldehyde functional groups. See Figure 2. This follows what is also taught in Ogle et al..

On the other hand, claims 1 and 16 disclose a tissue comprising a linker having one end bonded to the tissue and the other end to one end of a bridge molecule, while the other end of that same bridge molecule is bonded to one end of another linker molecule. Thus, a bridge molecule is bonded to two or more linkers. A linker links to the tissue on one end, and instead of linking to a different portion of the tissue on its other end, as taught in Ogle et. al. and Yang et. al., it is instead linked to a bridge molecule that is distinguished chemically from the linker.

While it is true that both Ogle et. al. and Yang et. al. teach the use of glutaraldehyde as a crosslinker, neither teach a tissue having glutaraldehyde linkers and bridge molecules that are chemically different from glutaraldehyde, that bond at least two of such linkers together. Ogle et. al. is concerned with a crosslinker having the correct size, such as glutaraldehyde or its polymerized oligomer, for such linking action, and the deficiency is not supplied by Yang et. al., as Yang et. al. also teaches the same crosslinked tissue linked by glutaraldehyde. See Figure 2. No bridge molecule, chemically different from the crosslinker, is mentioned or taught in Yang et. al., Therefore, the combined teaching of Ogle et al. and Yang et al. do not teach nor suggest

how to arrive at the subject matter of claims 1 and 16, and claims 1 and 16 are not obvious over Ogle in view of Yang et. al.

Claims 34 and 36 disclose bridge molecules bonded to two or more modified sites of the tissue. This is also not taught in Ogle et al.. This deficiency is also not supplied by Yang et. al., as noted above. In addition, Yang et al. teaches that glutaraldehyde can either be used to crosslink the tissue itself, or if amines are used to treat the tissue first to minimize calcification, glutaraldehyde can be used to crosslink the tissue via the modified sites, again only teaching the use of linkers alone, and not the use of bridges to link linkers. See Figure 2. These glutaraldehyde compounds are not first bonded to modified or unmodified tissue, and then further bonded to bridge molecules. Therefore, bridge molecules for bonding modified sites of the tissue are not taught by the combined teaching of Ogle et al. and Yang et al.

The Examiner suggests that after reacting with glutaraldehyde as disclosed in Ogle et al., it would have been obvious to react with a diamine and then with additional glutaraldehyde as suggested by Yang et al. to arrive at the claimed bridges. Applicants respectfully submit that this reasoning fails to recognize that in both Ogle et al. and Yang et al., one end of the glutaraldehyde molecule is linked to one part of the tissue and the other end to another part of the tissue, which in effect fixed the tissue with the crosslinker, leaving no free end of the crosslinker to be bonded to a bridge molecule. To cause one end of the crosslinker to be detached from tissue so that it can be bonded to a bridge molecule will require a different mechanism, and hence a different invention, than as found in the instant claims.

The examiner further noted that since the present specification discloses that the linker and bridge molecule can be applied to the tissue sequentially, if both ends of glutaraldehyde react with tissue, then this embodiment will not work since the tissue is contacted with glutaraldehyde in the absence of bridge molecule, as in Ogle et. al. and Yang et. al. Applicants respectfully submit that this point strengthens Applicants' position that the present invention is distinguished from the cited references. To fix a tissue requires the presence of a crosslinker having the desired size to span the gap between the sites. Ogle et al. screens for glutaraldehyde oligomers having the desired length to fix the tissue. Likewise, Yang et. al. fix the tissue using glutaraldehyde of the required size. They both concentrate on having a linker large enough to accomplish the goal. On the other hand, the present inventors recognize that reacting linkers not having the desired length to span the gap between the tissue sites allows the use of a bridge molecule to connect the free ends of at least two such linkers. This gives more options in the choice of bridge molecules for fixing tissues not contemplated by the cited references. If greater flexibility of the crosslinked tissue is desired, the bridge molecule chosen can include a saturated hydrocarbon backbone without any rings. See page 19, lines 5-7 of the specification. On the other hand, if a more rigid fixed tissue is desired, it can be accomplished by the addition of unsaturated bonds or rings to the bridge. See page 19, lines 8-10. This novel approach is not taught or suggested anywhere in the prior art.

Finally, the Examiner suggests that in the final step in Yang et al., the tissue is reacted with glutaraldehyde after reacting with a diamine, resulting in the diamine being the linker and the glutaraldehyde being the bridge molecule which will have one end coupled to an amine of a diamine already bonded to the tissue and the other end

coupled to an amine of another diamine that is bonded to the tissue at a different site. Applicants again respectfully traverse this point. Glutaraldehyde is a known linker or modifier of tissues, as taught in both Ogle et. al. and Yang et. al. Such linkers can polymerize spontaneously in solution, again as taught in Ogle et. al. Bridges, on the other hand, are not linkers and are chemically different from linkers, as taught in the present invention. There is no teaching or suggestion in either cited reference of how to modify glutaraldehyde so that it will not polymerize spontaneously. Contrary to the Examiner's contention, glutaraldehyde, a known crosslinker for tissue, does not fit the definition of a bridge molecule.

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or combination of references, must teach or suggest all the claim limitations. MPEP § 2142. Applicants respectfully submit that Yang et. al. does not supply the deficiency of Ogle et. al., as no bridge molecules, chemically different from linkers, or bridge molecules linking sites in tissues that have been modified, are suggested or taught by the combined teachings of Ogle et. al. and Yang et. al.. The prior art fails to disclose all the claim limitations.

Dependent claims 2-15 and 17-28, 35, and 37-43, which are dependent from independent claims 1, 16 , 34, and 36, respectively, were also rejected under 35 U.S.C. §103(a) as being unpatentable over Ogle et al.. (U.S. 5,958,669) in view of Yang et al.. (5,935,168).

While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 1, 16, 34 and 36. These dependent claims include all of the limitations of the base claims and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 2-15 and 17-28, 35, and 37-43 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 1-28 and 34-43 under 35 U.S.C. § 103(a) as being unpatentable over Ogle et al.. in view of Yang et al..

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

On page 2 of the Office Action, the Examiner noted that a Supplemental Information Disclosure Statement, Form 1449, and accompanying references filed on August 13, 2002 did not reach the application file. A separate Communication forwarding these documents is being mailed with this Amendment and Response.

If a telephone conference would be helpful in resolving any issues concerning this

communication, please contact Applicants' attorney of record, Hallie A. Finucane at (952) 253-4134.

Respectfully submitted,

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Date: September 22, 2003

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